IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: GOLDENBERG
Serial No.: 09/965,796
Filed: October 1, 2001
Title: IMMUNOTHERAPY OF B-CELL MALIGNANCIES USING ANTI-CD22 ANTIBODIES
Group Art Unit: 1643
Examiner: Alana M. Harris
Attorney Docket No.: IMMU:007US3
Confirmation No.: 3640

EFS-WEB

REPLY BRIEF UNDER 37 CFR §41.41

COMMISSIONER FOR PATENTS
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Sir:

This reply brief is being filed in accordance with the provisions of 37 C.F.R. § 41.41.

In the Answer the examiner has made a number of statements to which appellant wishes to respond. On page 16 of the Answer the examiner notes that she had provided appellants with a definition for the term "conventional" from Webster's Collegiate Dictionary as "developed, established, or approved by general usage: customary." She urges that appellants countered this definition with one from the American Heritage Dictionary of the English Language as "conforming to established practice or accepted standards: traditional." In point of fact, the two definitions are remarkably similar, and an investigational drug in Phase I clinical trials cannot be considered a conventional therapy by either definition. Such a drug neither "conform[s] to established practice or accepted standards" nor is "established, or approved by general usage." Therefore, the point is moot, as neither definition supports a conclusion that treatment with an antibody was "conventional therapy" in 1994.

The examiner follows her dictionary comment with a statement at the top of page 17 that "it is clear that at the time of filing the instant application, March 1997, CD22 antibodies had been in

use for at least 6 years and directed to treating B-cell malignancies." In this regard, she appears to rely on the publication by Dr. Goldenberg in *J. Clin. Onc.*, vol. 9, no. 4, pp. 548-564 (1991). However, a report in a Phase 1 trial of "two partial remissions, two mixed and minor responses, and one no response…in a series of five assessable therapy patients" hardly constitutes a basis for the conclusion that "CD22 antibodies had been **in use** for at least 6 years and **directed to treating** B-cell malignancies." It certainly does not raise the use of anti-CD22 antibodies to the status of "conventional" treatment.

The examiner's statement that she "reasonably regards the practice of combining two well-known and established antibodies as conventional therapy" is not supported by appropriate evidence in the record. She cites a first reference, Maloney, which discloses results from a ***Phase I clinical trial*** to evaluate the safety of anti-CD20 antibody as a single agent therapeutic. There is a comment in this reference that "extension of these studies to patients with minimal disease, using antibody alone or in combination with ***conventional therapies***, may provide the greatest benefit. "Conventional therapies" at the time of the Maloney article, circa 1994, were chemotherapies, not antibody therapies, and this has been established by appellants with declarations by three well-known experts in the field. The declarations all show that antibody therapies were not "conventional" in 1994, when Maloney published the cited article, and **this evidence stands unrebutted in the record.**

The examiner next proposes to combine the teaching in Maloney with a reference that discloses results from ***another Phase I clinical trial***, this time for radiolabelled anti-CD22 antibodies. She then urges that these two documents each disclose "conventional therapy," despite appellant's unrebutted evidence to the contrary. Moreover, above and apart from the conclusion that ***any single*** antibody therapy was conventional circa 1994, she finds that ***combination*** antibody therapy would have been obvious, even in the face of declarations from three well-known experts in the field that no combination antibody therapy has yet been approved and that even single antibody therapy was not considered to be conventional in 1994. In this regard, she states that "the teachings of Appellants' submission of published papers and declarations do not preclude one of ordinary skill in the art from combining two antibody compositions with established known functions." Of course, a skilled artisan is not "precluded" from doing anything, but the issue is whether it would have been obvious to do what Appellants have done in light of the teaching of the art and the present record. The unequivocal answer to that question is a resounding NO.

Finally, the examiner again urges that "Appellants reference CD22 antibodies, which are not the same as those referenced in the prior art." However, the antibodies in the articles proffered by

appellants to show the unobvious results achieved when antibodies are combined as specified in appellants' claims are epratuzumab, rituximab and IMMU-106, and ***are*** the same as those referenced in the prior art. U.S. 5,789,554 discloses chimerized and humanized LL2 antibodies denoted cLL2 (mouse/human chimeric mAb) and hLL2 (humanized mAb), respectively, which include the CDRs of murine monoclonal antibody LL2. Epratuzumab is humanized LL2 (hLL2). Rituximab is the antibody disclosed in Maloney. IMMU-106 is a humanized anti-CD20 antibody, the heavy chain CDR3 of which differs from the rituximab disclosed in Maloney (rituximab having the sequence STYYGGDWYFNV and IMMU-106 having the sequence STYYGGDWYFDV). Thus, the results reported in these articles are highly probative.

One of the articles submitted by Appellants relates to results with epratuzumab and rituximab. The other articles reports results with epratuzumab and IMMU-106. The articles show the unexpected results that are achieved with the present combination of antibodies. They are a comparison to "the prior art" and are not a comparison to an antibody that is "distinct" from the antibody of Appellants' claims.

For these reasons and those presented in the brief on appeal, the Board is requested to reverse the decision of the examiner and pass the present case to issuance.

Respectfully submitted,

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NOVEMBER 27, 2008
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